REMARKS/ARGUMENTS

Status of the Claims

Claims 1-35 were rejected. Claims 12, 27, and 31 have been canceled. Claims 1-11, 13-19, 21-30, and 32-35 have been amended. Claims 1-11, 13-26, 28-30, and 32-35 are pending.

Amendments to the Claims

Claims 1-11, 13-19, 21-26, 28-30, and 32-35 have been amended to correct antecedent basis.

Claims 1 and 21 and their respective dependent claims have been amended to recite a "filter". Support for this amendment can be found throughout the specification and in the originally filed claims. See, for example, page 12, lines 15-26. The amendment was made to clarify the claimed subject matter and does not narrow the scope of the claims.

Claim 19 has been amended to recite a "hepatitis A" viral titer. Support can be found, for example, on pages 29 and 30 of the specification.

Claim 24 has been amended to recite a "viral particle of less than 70 nm in size". Support for this amendment can be found throughout the specification and in the originally filed claims. See, for example, claim 27.

No new matter has been added by way of these amendments.

Amendments to the Specification

The specification was amended to contain the standard terminology for the priority claim under 35 U.S.C. §119(e). Accordingly, the objection to the specification should be withdrawn.

Objections to the Claims Should Be Withdrawn

Claim 31 was objected to for a misspelled word. Claim 31 has been canceled and the objection has been obviated.

Claim 32 was objected for improper antecedent basis for "a mammal". Claim 32 has been amended to correct this error and the objection has been obviated.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-35 were rejected under 35 U.S.C. §112, second paragraph, for being indefinite. This rejection is respectfully traversed.

Claims 1 and 21 were rejected as being indefinite for not having agreement between terms recited in the preamble and in the final method step. Claims 1 and 21 have been amended to have agreement between the preamble and the final method step. The amendment to the claim obviates the rejection.

Claims 1, 2, and 19 were rejected for improper antecedent basis for the term "antioxidant enzyme". Claims 1, 2, and 19 have been amended to correct the antecedent basis of this term and the rejection should be withdrawn.

Claims 4 and 12 were rejected for reciting a trademark. Claims 4 and 12 have been amended and no longer recite the trademark and therefore rejection has been obviated.

Claim 11 was rejected for the term "at least one second filtration means." Claim 11 has been amended to recite "a second filter." The amendment to claim 11 obviates the rejection.

Claim 35 was rejected for lack of proper antecedent basis. The claim has been amended to have proper antecedent basis and the rejection should be withdrawn.

In light of the comments above and the amendments to the claims, claims 1-35 satisfy the requirements U.S.C. §112, second paragraph, and the Examiner is respectfully requested to withdraw the rejection.

The Rejection of the Claims under 35 U.S.C. §102 Should Be Withdrawn

Claims 22-35 were rejected under 35 U.S.C. §102(a) as being anticipated by Privalle *et al.* (2000) *Free Radical Biology & Medicine 28*:1507-1517. This rejection is respectfully traversed.

Claims 22-26 and 28-30 are drawn to a "chemically modified hemoglobin solution comprising at least one endogenous antioxidant enzyme, wherein said chemically modified hemoglobin solution comprises a POE linkage, said endogenous antioxidant enzyme retains enzymatic activity, and said chemically modified hemoglobin solution is substantially free of viral contamination." Claims 31-35 are drawn to various methods employing the novel chemically modified hemoglobin solution of the instant invention. The Examiner asserts that

since the PHP compositions of Privalle *et al.* are described as being used in Phase II and Phase III clinical trials, "they are deemed inherently to be free of viral contamination to the same extent claimed by Applicants." See, page 5, lines 2-3 of the Office Action, mailed March 5, 2003. The Examiner concludes that the reference anticipates the compositions and methods set forth in claims 22-35.

A *prima facie* case of anticipation under 35 U.S.C. §102 has not been established. An anticipatory prior art publication must contain within its four corners a sufficient description to enable a person of skill in the art to make the invention without an unreasonable amount of experimentation (*Advanced Display systems Inc. v. Kent State University* 212F.3d 1272,1282). Privelle *et al.* does not satisfy this requirement. Privelle *et al.* does not disclose the method by which the PHP molecules employed in the Phase II and III clinical trials were prepared. While the use of the PHP molecules described in Privelle *et al.* in clinical trial implies they have a low concentration of viral particles, the references provides no guidance regarding how such compositions can be made and retain the properties of the molecules set forth in claims 22-35 of the instant invention. As one of skill in the art would find not guidance regarding how such a molecule could be made, claims 22-26 and 28-35 are novel in view of Privelle *et al.* (2000) and the rejection of the claims under 35 U.S.C. §102(a) should be withdrawn.

Claims 22-35 were rejected under 35 U.S.C. §102(b) as being anticipated by Privalle *et al.* (1999) *Free Radical Biology & Medicine*, 6th Annual Meeting, Abstract No. 254. This Rejection is respectfully traversed.

The Abstract of Privalle *et al.* (1999) states that PHP is a modified hemoglobin currently in clinical trials. The Examiner concludes that the PHP compositions referenced in Privalle *et al.* (1999) are deemed to be "inherently free of viral contamination to the same extent as applicants claimed composition." However, Privalle *et al.* (1999) provides no guidance regarding how the recited PHP composition can be made and retain the properties of the molecules set forth in claims 22-35 of the instant invention. Anticipatory art under 35 U.S.C. §102 must be an enabling disclosure. As one of skill in the art would find no guidance regarding how such a molecule could be made, claims 22-26 and 28-35 are novel in view of Privelle *et al.* (1999) and the rejection of the claims under 35 U.S.C. §102(b) should be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103 Should Be Withdrawn

Claims 22-35 were rejected under 35 U.S.C. §103(a) as being obvious in view of Privalle *et al.* (2000) *Free Radical Biology and Medicine 28*:1507-1517 and as obvious in view of Privalle *et al.* (1999) *Free Radical Biology & Medicine*, 6th Annual Meeting, Abstract No. 254. This rejection is respectfully traversed.

Claims 22-26 and 28-30 are drawn to a "chemically modified hemoglobin solution comprising at least one endogenous antioxidant enzyme, wherein said chemically modified hemoglobin solution comprises a POE linkage, said endogenous antioxidant enzyme retains enzymatic activity, and said chemically modified hemoglobin solution is substantially free of viral contamination." Claims 31-35 are drawn to various methods employing the novel chemically modified hemoglobin solution of the instant invention. The Examiner asserts that it would have been obvious at the time of instant invention to "subject the PHP of Privalle *et al.* to any known or combination of known purification procedures in order to reduce the viral contamination of the PHP, because it is known that blood products are susceptible to viral contamination, because it is desirable in the art to minimize viral contamination of all medical products to improve their safety, and because the use of the known purification procedures in order to achieve only expected purification is *prima facie* obvious." Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

A *prima facie* case of obviousness requires a reasonable expectation of success. The disclosure of Privalle *et al.* (1999) and Privalle (2000) does not satisfy this requirement. As outlined above, Privalle *et al.* does provide an enabling disclosure as to how the PHP molecule is prepared. For example, neither Privalle *et al.* (1999) nor Privalle *et al.* (2000) provide guidance regarding how a hemoblogin composition having POE linkages could be prepared to allow retention of endogenous antioxidant enzymes that retain antioxidant activity and to be substantially viral free. Accordingly, Privalle *et al.* (2000) and Privalle *et al.* (1999) fails to generally place the needed subject matter supporting the obviousness rejection in the public domain prior to the present invention.

Moreover, the rejection under 35 U.S.C. §103 fails to provide art that would supplement this deficiency in the *prima facie* case of obviousness. Instead, the Examiner broadly asserts that

one of skill in the art could subject the PHP of Privalle *et al.* to "any known combination of known purification procedures in order to reduce the viral continuation of PHP." This assumption is incorrect. A *prima facie* case of obviousness requires a reasonable expectation of success. The Examiner's assertion that any procedures known to reduce viral contamination would produce a substantially free composition as claimed by the instant invention is in error. In fact, as outlined on page 3, lines 17-23 of the specification "a serious problem associated with animal or human derived hemoglobin based blood substitutes arises from the possibility of viral contaminants in the modified hemoglobin solution. Virus elimination and inactivation is commonly performed using either chromatography or heat inactivation. However, treatment of hemoglobin solutions using these methods either removes or abolishes the beneficial activity of the antioxidants associated with the hemoglobin molecule." Contrary to the conclusions set forth in the Office Action, one of skill in the art would not extrapolate from the teachings of Privelle *et al.* how the claimed hemoglobin composition is made; nor would one of skill simply assume any known method for viral decontamination would be successful in producing a chemically modified hemoglobin solution comprising at least one endogenous antioxidant enzyme, where the modified hemoglobin comprises a POE linkage, *the endogenous antioxidant enzyme retains enzymatic activity, and the solution is substantially free of viral contamination*. Accordingly, the Examiner's assertion that the common knowledge is sufficient to render the claimed compositions and method obvious does not in and of itself make it so, absent evidence of such knowledge.

In fact, prior to the present invention methods of preparing the claimed composition set forth in claims 22-35 was not taught or suggested by the art. In fact, as outlined in Example 2, on page 25, lines 28 of the specification, the present invention successfully employs a filtration system that decreases endotoxin activity to less than 1 EU/ml, and further demonstrates the removal of various models of virus including HIV, BVD, and HAV. See, Example 4 and Table 6. Thus, prior to the present invention it was not know how to prepare a composition as claimed by the instant invention, and accordingly, the prior art as a whole could not have placed the claimed invention of claims 22-26 and 28-35 in the hands of the public and a *prima facie* case of obviousness under 35 U.S.C. §103 has not been established.

In view of the comments above, Applicants respectfully request that the rejection of claims 22-26 and 28-35 under 35 U.S.C. §103 as obvious in view of Privelle *et al.* (1999) and Privalle (2000) be withdrawn.

Comments Regarding Examiner's Reasons for Allowance

The Examiner states claims 1-21 would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. §112, second paragraph. As discussed above, as amended, claims 1-21 satisfy the requirements of 35 U.S.C. §112, second paragraph and are in condition for allowance. While the art employed filters capable of producing a filtrate having hemoglobin and endogenous antioxidant enzymes, the art does not teach or suggest a method of preparing a chemically modified hemoglobin solution comprising an endogenous antioxidant enzyme that retains antioxidant activity and is substantially free of viral contamination as recited in claim 1. In addition, the art does not teach or suggest a method of preparing a modified hemoglobin solution comprising an endogenous antioxidant enzyme where the composition is substantially free of viral contamination and prepared by the methods as recited in claim 21.

Consideration Of Previously Submitted Information Disclosure Statement

The Examiner indicates that copies of Citation Nos. 30 and 39 provided in the IDS filed on February 1, 2002 were not received by the U.S. Patent and Trademark Office. Applicants attach herewith copies of Privalle *et al.* (1997) "Pyridoxalated Hemoglobin Polyoxyethylene (PHP): A Nitric Oxide Scavenger with Antioxidant Properties," 4th Annual Meeting of the Oxygen Society and D'Agnillo *et al.* (1993) *Biomat., Art. Cells & Immob. Biotech.*, pp. 609-621, Vol. 21(5). The Examiner is respectfully requested to consider the references and return an initialed copy of the PTO Form 1449. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statement and the Form 1449 are attached hereto.

CONCLUSIONS

The Examiner is respectfully requested to withdraw the rejections and allow claims 1-11, 13-26, 28-30, and 32-35. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the US Patent and Trademark Office at Fax No. (703) 872-9306 on the date shown below.

Rebecca Kerney — 8/5/03

Rebecca Kerney — Date